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Distant Skin and Soft Tissue Metastases From Sarcomas

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Background and Objectives: This small series documents the clinical and pathological features and the rarity of distant skin and soft tissue metastases from sarcomas.

Materials and Methods: Five cases of sarcomas from different anatomical locations that had metastasized to skin and subcutaneous soft tissue were identified in three women and two men. The age range was 41–77 years. The primary tumors had wide excisions, followed by either radiation or chemotherapy, or both. The histological types were epithelioid sarcoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, and leiomyosarcoma. Metastases occurred to the skin and soft tissue of the chest wall, leg, breast, and abdominal wall. The diagnosis was established by excision biopsies for three cases and by needle biopsy and fine-needle aspiration for two cases.

Results: Three patients died within 7 months of the diagnosis of soft tissue metastases that were always histologically high grade and never solitary. One patient is alive with lung metastasis discovered 17 months after excision of primary. Lung metastases occurred either simultaneously or within a short period after soft tissue metastases.

Conclusion: Distant skin and soft tissue metastases from sarcomas are very rare and often occur as a terminal event.

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KEY WORDS: sarcoma; distant metastases; skin; soft tissue

INTRODUCTION

Sarcomas are rare tumors of the connective tissue; those arising in the soft tissue constitute less than 1% of all malignancies. They represent a diverse group of mesenchymal neoplasms that, unlike epithelial malignancies, rarely metastasize to the lymph nodes and brain. Hematogenous metastases to the lungs are common [1–5]. Distant soft tissue and cutaneous metastases are very rare. We report four patients with soft tissue sarcoma and one case of uterine sarcoma with unusual sites of metastases to distant soft tissues. The significance of these lesions is discussed, with a review of the pertinent literature.

MATERIALS AND METHODS

Approximately 320 cases of sarcomas from all sites, including the extremities, retroperitoneum, gastrointestinal tract, skin, and rarely, the uterus, were seen in the Department of Pathology at the University of Pittsburgh Medical Center (UPMC), Pittsburgh, Pennsylvania; 150 cases of soft tissue sarcoma cases were seen in the Department of Surgical Oncology (by C.P.K.) at Millard Filmore Hospitals, Buffalo, New York, over a 5- and 3-year period, respectively. The common histological types in order of frequency were liposarcoma, leiomyosarcoma, malignant fibrous histiocytoma, Kaposi sarcoma, and synovial sarcoma. Other less common subtypes included epithelioid sarcoma, Ewing sarcoma, and osteogenic sarcoma. A total of five cases of sarcomas

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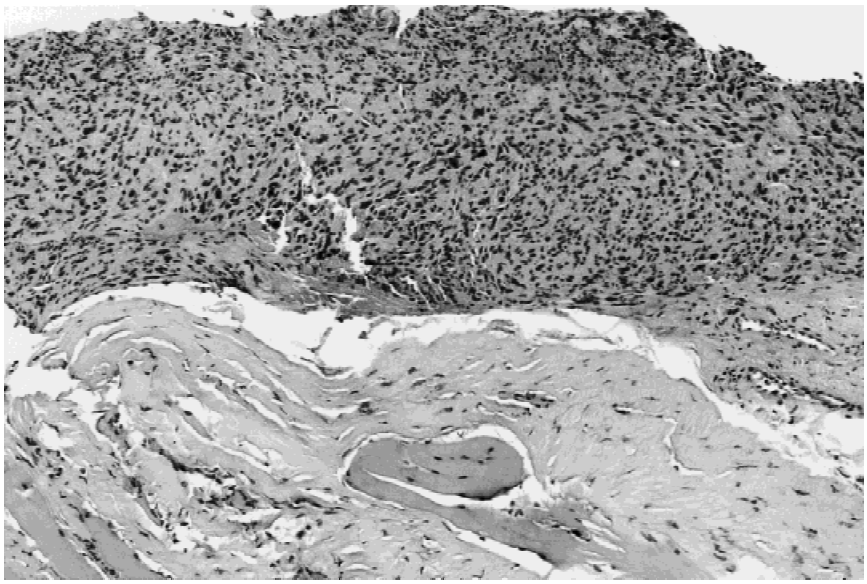

Fig. 1. Case 1, demonstrating soft tissue metastasis from the uterine sarcoma. Immunohistochemical staining displayed strong positivity with desmin (H&E ×110).

with distant skin (one case) and soft tissue metastases (four cases) were identified. These tumors occurred outside the operative field; they did not represent local recurrences or direct extension into skin from the primary tumor. The diagnosis was established on excised specimens in three cases and by needle biopsy and aspiration, respectively, in two cases. The clinical findings, treatment, and pathological findings are summarized below.

All excised specimens were fixed in 10% formalin and representative sections embedded in paraffin. To confirm the diagnosis, 5-μm-thick sections were stained with hematoxylin and eosin (H&E), as well as by standard immunohistochemical techniques, when necessary. The following antibodies were used S100 (dilution 1:300), Desmin (dilution 1:100), HMB45 (dilution 1:50), and EMA (dilution 1:25) [Dako, Carpentaria, CA]; AE1/3 (dilution 1:500) [Boehringer Mannheim, Indianapolis, IN].

Case 1

A 63-year-old woman presented with vaginal bleeding. Her outside workup led to a total abdominal hysterectomy and bilateral salpingoophorectomy in June 1993. Pathologic examination revealed a 5-cm high-grade uterine leiomyosarcoma. One year later bilateral lune metastases developed. She was treated with doxorubicin/ifosfamide-based chemotherapy for three cycles without tumor response and was subsequently referred to UPMC. She completed her chemotherapy but was noted to have disease progression within her lungs, as well as new subcutaneous lesions within the anterior abdominal wall. The diagnosis of sarcoma was confirmed after a needle biopsy of the abdominal mass (Fig. 1). The patient expired in July 1995, 7 months after the diagnosis of subcutaneous metastases.

Case 2

A 41-year-old woman underwent wide excision of a 8-cm malignant fibrous histiocytoma of her left buttock. Histologically, the tumor was mitotically active; it was composed of spindle as well as single and multinucleated giant cells and was scant; and in areas, the tumor had a storiform pattern. Six months later, the patient experienced a local recurrence and was treated with re-excision and postoperative radiation treatment to the thigh. About 8 months later, she underwent staged thoracoscopic wedge resection of the left, and then right, pulmonary metastases, and was considered disease free; histologically, the lung masses (Fig. 2A) were similar to the primary tumor. Two months later, follow-up computer tomography (CT) of the chest showed evidence of a new left upper lobe nodule, as well as a discrete soft tissue mass within the left breast. Needle aspiration of the breast lesion showed metastatic sarcoma (Fig. 2B). Further chemotherapy was unsuccessful, and the patient expired in late June 1995 of progressive respiratory compromise, 7 months after the appearance of soft tissue metastasis.

Case 3

A 77-year-old white man presented with right thigh and arm nodules that proved to be grade I–II leiomyosarcomas on excisional biopsies, August 1995. Microscopic necrosis was present. These tumors did not involve the skin and were confined to the subcutaneous soft

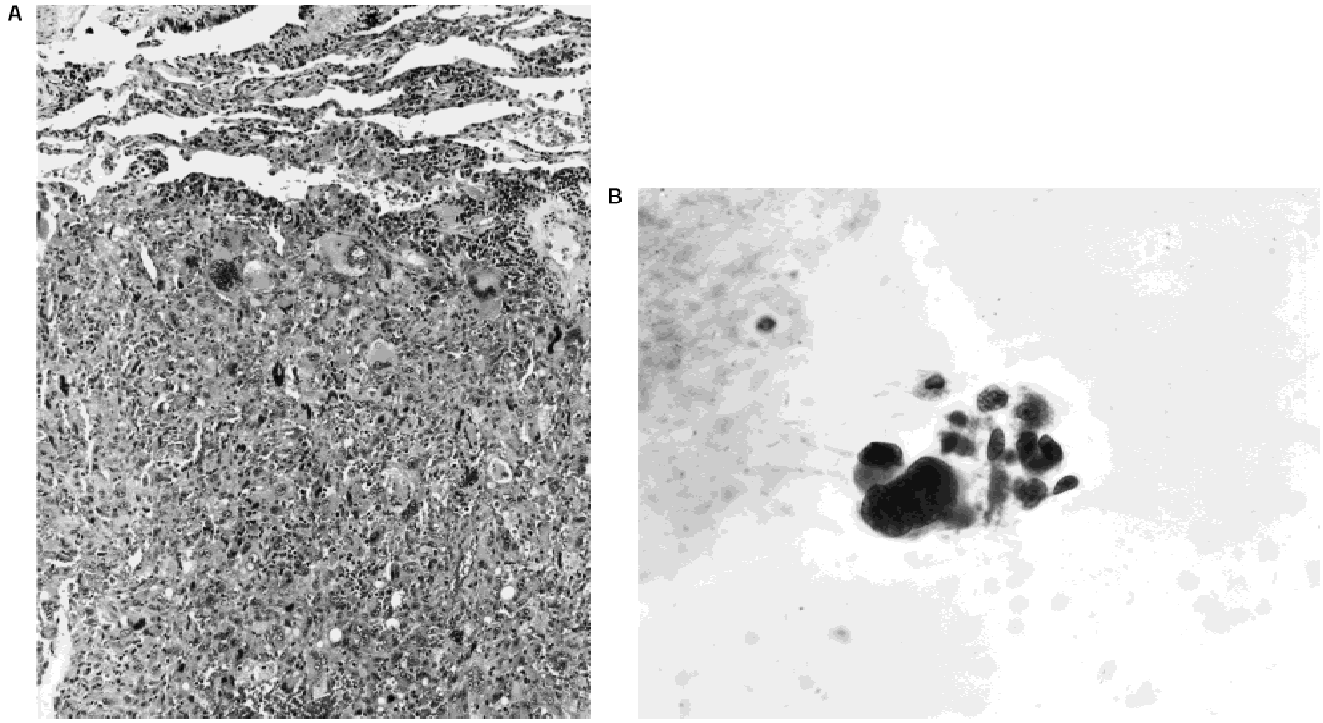

Fig. 2. Case 2, demonstrating lung metastasis from malignant fibrous histiocytoma of left posterior thigh. **A:** Tumor is cytologically pleomorphic and contains many tumor giant cells. (H&E, ×115.) **B:** Needle aspirate of the breast lesion demonstrates similar tumor giant cells. (Papanicolaou stain, ×240.)

tissue (Fig. 4). A CT scan of the chest, abdomen, and pelvis showed a retroperitoneal 4.5 × 3.5-cm tumor arising from the anterior wall of the inferior vena cava below the renal veins, which was resected with a portion of the inferior vena cava. Histologically, the retroperitoneal tumor was identical to the subcutaneous nodules; it was composed of interlacing bundles of spindle cells with eosinophilic cytoplasm and blunt-ended elongated nuclei, resembling smooth muscle cells. No necrosis or nuclear pleomorphism was noted. Mitoses averaged 5 per 10 high-power fields (hpf). Postoperatively, he received ifosfamide, dacarbazine, and cisplatin. At 17 months since operation, pulmonary metastases were detected on CT scan that were not visible on plain chest radiographs; the patient remains asymptomatic.

Case 4

A 66-year-old woman was treated with local radiation and systemic chemotherapy for an epithelioid sarcoma of the soft tissue of the arm in 1977. In 1991, she underwent an above elbow amputation for local recurrence. Three years later, metastases were found in the ipsilateral axillary lymph nodes, soft tissue of the chest wall, skin of scalp and in both lungs on chest radiography. The metastases apparently responded to chemotherapy, but she suffered a cerebrovascular accident and, when last seen in November 1995, she had persistent cutaneous tumor, but no tumor cells were demonstrated in a bronchial lavage specimen. The slides of the primary tumor are not available. The recurrent tumor in the skin was biopsied, and it showed clusters of ovoid to spindle cells in the dermis, which were negative with immunostains S-100 and HMB45. Tumor cells were focally positive for cytokeratin (AE1/3), vimentin, and EMA. No necrosis was seen; numerous mitotic figures were present. The histological features and the staining patterns were in keeping with a diagnosis of epithelioid sarcoma (Fig. 3).

Case 5

A 76-year-old man had resection of a left axillary mass that had recently increased in size. It was classified as a high grade malignant schwannoma based on foci of strong positive immunostaining with S-100 protein. Tumor was negative with actin and cytokeratins (AE1/3). No melanin was seen. The first local recurrence was resected and was followed by postoperative radiation therapy. The tumor recurred 3 months later distal to the operative site; lung metastasis were subsequently found. Despite chemotherapy, which included doxorubicin, several cutaneous and subcutaneous metastases developed in the chest wall, buttock, and thigh, which were resected. The patient died 2 months after appearance of the subcutaneous metastases. The patient had no history or clinical findings of neurofibromatosis.

Fig. 3. Recurrent epithelioid sarcoma of the arm in case 4 demonstrating plump spindle and ovoid cells forming ill-defined clusters in the dermis. These were negative with S-100 protein and HMB45 and focally positive with EMA, and AE1/3. (H&E, ×115.)

DISCUSSION

It is recognized that in soft tissue sarcoma, tumor size, grade, and superficial versus deep location, as well as some histological subtypes, such as leiomyosarcoma, are factors that predict risk of distant metastases and outcome [6]. Data concerning risk of soft tissue or skin metastases are scarce because of the rarity of this event. In our four patients, including the patient with uterine leiomyosarcoma, the tumors were histologically high grade and developed synchronous lung metastases. These patients survived less than 1 year after subcutaneous metastases were diagnosed. In case 3, the longer survival is probably related to histological grade and mode of treatment, although this patient was found to have lung lesions at his last follow-up visit.

Understanding the patterns of metastases in sarcoma is important if we are to design effective treatment regimens. Sarcomas metastasize most frequently to the lungs and liver. In about 40% of cases of soft tissue sarcoma, metastases occur solely to the lungs, excision of which can result in improved survival. Unresectable pulmonary metastases or extrapulmonary metastases have a uniformly poor prognosis [1–5,7]. Metastases to the lymph nodes are uncommon and occur in 2.6% of cases; this scenario is associated with poor prognosis [8]. Regional lymph node (34%) as well as distant metastases, especially to the scalp (22%), occur in epithelioid sarcoma [9] and our case 4 exemplifies this feature of this very rare sarcoma. In a review of autopsy studies of all types of malignancies, including leukemia and lymphoma, skin metastases occurred in 0.7–9% of malignancies; of these, sarcomas accounted for 2–3% of cases and were represented by a variety of cell types, including leiomyosarcoma, rhabdomyosarcoma, fibrosarcoma, chondrosarcoma, Ewing sarcoma, osteosarcoma, epithelioid sarcoma, and several undifferentiated sarcomas [10,11]. In a large series of 724 patients that excluded autopsy findings and deeply located soft tissue metastases, cutaneous metastases to the face, scalp, trunk, and pelvis from sarcomas of histological types almost identical to that reviewed earlier, occurred in 15 men and 4 women [12]. Cutaneous metastasis often occurred late in the course of the disease and carried a poor prognosis. With some epithelial malignancies, this may be the first manifestation of internal malignancy. However, it is very unusual for a deeply located sarcoma, as in our case 3, to present with subcutaneous metastases as an initial event. Skin metastases from spindle cell sarcoma might pose difficulties in histological diagnosis. An immunohistochemical stain panel using S-100, cytokeratins, and muscle markers, along with electron microscopy, will prove useful in ruling out metastatic melanoma and spindle cell carcinomas in most instances.

In two large series of patients with soft tissue sarcomas of a variety of histological types, deep soft tissue metastases occurred in 1.2% and 6.6% of cases, respectively [13,14]. No patient with distant subcutaneous metastasis was alive at 5 years. The median survival was 11.5 months, in contrast to 33% 5-year survival in patients with local recurrence only [13]. The vast majority of sarcomas will metastasize to lungs via a hematogenous route, but the mode of dissemination in some sarcomas may be dependent on histological subtype and grade [14]. In malignant fibrous histiocytoma, occasional skin and subcutaneous soft tissue metastases are mentioned, but usually as a terminal event [15,16]. A prevalence of deep soft tissue metastases has been noted especially to the retroperitoneum and omentum in some extremity myxoid and round cell liposarcomas. In an analysis of 60 extremity liposarcomas [17] occurring over a 19-year period, initial extrapulmonary metastatic sites included seven cases of soft tissue metastases to the axilla, breast, abdominal wall, and other sites. However, it should be noted that, in this series, more than 50% of cases with unusual metastatic sites were high-grade round cell and pleomorphic types. Although this study did not find a relationship between histologic subtype and extrapulmonary metastasis, some patients with extrapulmonary me-

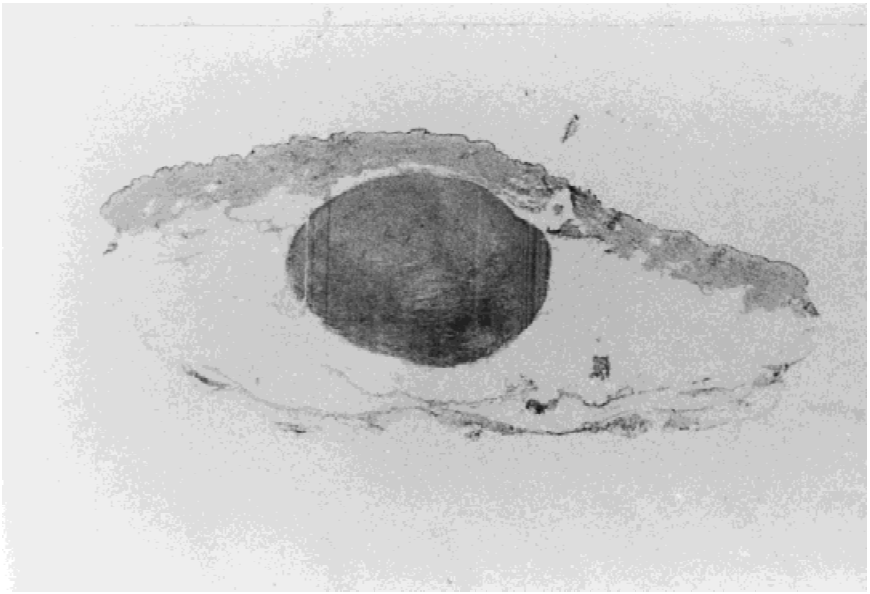

Fig. 4. Subcutaneous metastasis from leiomyosarcoma of the inferior vena cava in case 3. (H&E, ×10.)

tastases achieved longer disease-free survival. It was suggested that the survival benefit might be related to resection of an initial metastasis if it was an isolated event; in such instances, the possibility of a multifocal sarcoma should be kept in mind; however, the extreme rarity and the presence of metastases elsewhere and histological similarity to the primary tumor preclude that diagnosis [18].

The pattern of metastasis in uterine sarcomas has been analyzed in an autopsy study; no cutaneous or soft tissue metastases were described [19]. In examining a series of 28 patients with uterine sarcomas, Jones and Norris [20] found a rare instance of metastasis to skeletal muscle at autopsy only; the location has not been specified. In uterine sarcomas, it was rare for distant metastasis to occur without an initial local recurrence.

Distant skin and soft tissue are unusual sites of metastasis from all sarcomas; these metastases are seen as a late event, often associated with systemic metastases, particularly to the lungs. Survival is generally poor and may be related in part to histological subtype and grade. Our five patients with sarcomas metastatic to distant soft tissue, skin, and subcutis, representing cases collected from two institutes, emphasize this issue. The benefit of different modalities of treatment for skin and soft tissue metastasis is unknown, accentuating the need for future studies.

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